INTRODUCTION TO THE HISTORY

OF

THE ARMED FORCES MEDICAL UNIT IN KUALA LUMPUR

MALAYA

AND

THE ARMED FORCES RESEARCH INSTITUTE OF MEDICAL SCIENCES

(AFRIMS)

IN BANGKOK, THAILAND

BY

THEODORE E. WOODWARD, M.D., M.A.C.P.

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IN BANGKOK, THAILAND

To Margaret
With Best Wishes
and Congratulations for
her remarkable
contributions in the course
of Microbiology
Sincerely
T.E. Woodward
July 1987

BY

THEODORE E. WOODWARD, M.D., M.A.C.P.

There are a number of examples of bi-national medical science programs which have contributed significantly to public health. Among them are the Walter Reed Medical Research Unit in Kuala Lumpur, Malaya, and the Armed Forces Research Institute of Medical Science (AFRIMS) in Bangkok, Thailand. The Malaysian Program had its beginnings in 1948. The SEATO Medical Research Laboratory in Bangkok, which had its debut in 1959, was the forerunner of AFRIMS. Also, in 1959, the SEATO Cholera Research Laboratory was established in Dacca (East Pakistan). The United States-Japan Cooperative Medical Science Program, which was much broader in its scientific scope, began in 1965. Each of these governmental programs were conceived as similar in their objectives, namely to improve the health of peoples pressing in adjacent Asian areas elsewhere.

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KUALA LUMPUR

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KUALA LUMPUR

Background

The research program in Malaya began as a sequel to the vision, wisdom and hard work of Joseph E. Smadel. Following World War II, his work as Scientific Director of WRAIR, along with a talented staff of qualified investigators, elevated and

Figure 1. Joseph E. Smadel, M.D. Picture taken about 1962 during his tenure as Deputy Director of the National Institutes of Health.

maintained that Institute as one of the world's leading research centers for the study of

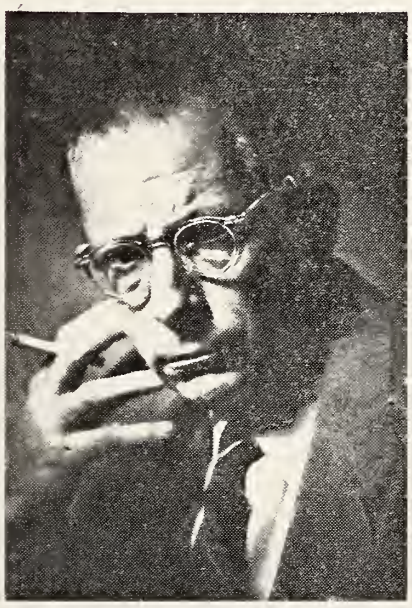

Figure 1. Joseph E. Smadel, M.D. Picture taken about 1962 during his tenure as Deputy Director of the National Institutes of Health.

infectious diseases. Events in the Pacific Theater of War provided a disturbing enigma for the Allied Forces particularly with respect to death and morbidity caused by scrub typhus fever and malaria. From 1941 to 1945, approximately 18,000 cases of scrub typhus were reported among allied servicemen in the southwest Pacific and China-Burma-India Theater. Fatality rates in different epidemics varied from as low as 0.6 per cent in some regions to as high as 35 per cent in others. Neither a preventive vaccine or a specific form of treatment was available. Attack rates diminished when mite control measures were better understood and applied appropriately.

Joe Smadel had a working arrangement with Parke Davis and Company in Detroit, to send any new anti-microbial drugs which exerted even the slightest inhibitory effect for viral and rickettsial agents. Along with other drugs, Dr. Fred Stimpert

transmitted a small supply of Chloromycetin, a newly tested antibiotic isolated by Dr. Paul Burkholder of Yale. When tested in fertile hens' eggs and mice by Betty [illegible] Joe's devoted Research Associate, this new antibiotic showed some anti[illegible] activity, against lymphogranuloma venereum virus and **Rickettsia orientalis** (tsutsugamushi) the cause of scrub typhus. These promising findings were followed by preparation of larger quantities of the new substance, evaluation of its pharmacologic properties [illegible] WRAIR (ref.) and subsequent clinical testing in a few cases of typhus in Mexico [illegible] epidemic typhus in Bolivia (ref.). Scrub typhus never continued as a [illegible] [illegible] at and a therapeutic [illegible] of its record of defeat [illegible] [illegible] ability to control the disease [illegible].

Through Joe Smadel [illegible] Rufus Holt, Commandant [illegible] [illegible] al Department Research and Graduate School (now WRAIR), [illegible] [illegible] ent and request for the conduct of a clinical trial in Malaya. Initially, [illegible] given to conducting a scrub typhus clinical trial in Indonesia; political [illegible] [illegible] cluded this possibility. Dr. Raymond Lewthwaite, one of the world's [illegible] [illegible] orities in the field of scrub typhus, was then Director of the Institute [illegible] [illegible] arch at Kuala Lumpur (K.L.), where much of the basic work on the disease [illegible] [illegible] red. Through appropriate administrative channels, an invitation [illegible] visit K.L. for the purpose of conducting a clinical trial was consum[illegible]

transmitted a small supply of Chloromycetin, a newly tested antibiotic isolated by Dr. Paul Burkholder of Yale. When tested in fertile hens' eggs and mice by Betsy Jackson, Joe's devoted Research Associate, this new antibiotic showed some anti-bacterial activity, against lymphopathia venereum virus and **Rickettsia orientalis** (tsutsugamushi), the cause of scrub typhus. These promising findings were followed by preparation of larger quantities of the new substance, evaluation of its pharmacologic properties at WRAIR (ref.) and subsequent clinical testing in a few cases of typhus in Mexico (ref.) and epidemic typhus in Bolivia (ref.). Scrub typhus fever continued as a central disease threat and a therapeutic disappointment because of its record of defeat with respect to inability to control the disease or prevent death.

Through Joe Smadel's stimulus, Col. Rufus Holt, Commandant at the Army Medical Department Research and Graduate School (now WRAIR)), transmitted a letter of intent and request for the conduct of a clinical trial in Malaya. Initially, consideration was given to conducting a scrub typhus clinical trial in Indonesia; political unrest there precluded this possibility. Dr. Raymond Lewthwaite, one of the world's recognized authorities in the field of scrub typhus, was then Director of the Institute for Medical Research at Kuala Lumpur (K.L.) , where much of the basic work on the disease had been conducted. Through appropriate administrative channels, an invitation for a medical team to visit K.L. for the purpose of conducting a clinical trial was consummated.

ARMY MEDICAL CENTER **RLH/es**
Army Medical Department Research and Graduate School
Washington 12, D. C.

MEDEC-ZA 21 October 1947

Dr. R. Lewthwaite, Director
Institute of Medical Research
Kuala Lumpur, Malaya

Dear Doctor Lewthwaite:

I am writing you at the suggestion of General Hood concerning the possibilities of setting up an experimental program in your area to test the value of a new antibiotic, chloromycetin, as a therapeutic agent in the treatment of scrub typhus and other rickettsial diseases. This compound shows great promise in scrub typhus. It appears to be far superior to Paba in treatment of this disease as produced experimentally. I am forwarding a chart and carbon copy of an article which is to appear in "Science" shortly. These will give you an idea of where we stand at the present time in the investigation.

We have just completed an adequate field experiment on the efficacy of scrub typhus vaccine, rat tissue type, in the prevention of this malady. Our vaccine failed to protect and we have given up the idea of trying to develop an effective vaccine, at least for the present.

For the field investigation of this product we will need only 40 cases of scrub within a period of about three months, half of which would act as controls. All cases would need to be hospitalized and the controls should, if possible, be treated without specific chemotherapeutic medication.

As for our part we would expect to provide all needed supplies, all needed laboratory personnel and one medical laboratory consultant to assist the regular war medical officers with diagnosis, treatment and evaluation.

Would you kindly consider the possibility of providing us with facilities for this experiment under conditions approximately as stated and inform me of the possibilities. The work could start at such time as the needed cases and facilities could be made available to us.

We are not asking that you commit yourself or your government in this matter at this time. If you agree that the experiment is possible then I should outline the matter completely and institute a formal request for approval by the U. S. Government and your own government.

Naturally the project, if carried out, will be a combined one between the two groups involved and the findings will be made available to your group and to your government if you so desire.

Will you kindly consider this matter as informal and unofficial until such time as we may make formal application for permission to perform the experiment.

Very truly yours,

RUFUS L. HOLT
Colonel, Medical Corps
Commandant, AMDRGS

1 Incl
Ms. "Chloromycetin, an Antibiotic with Chemotherapeutic Activity in Experimental Rickettsial and Viral Infections," with 1 chart

Air Mail.

INSTITUTE FOR MEDICAL RESEARCH
KUALA LUMPUR
MALAYA
November 18th, 1947

Colonel Rufus L. Holt,
Commandant,
Army Medical Department Research & Graduate School
Army Medical Center
Washington 12, D. C.,
U.S.A.

Dear Colonel Holt,

On my return from England, early this week, I found awaiting me your letter of 21st October, and its enclosures, relating to the projected field trial in Malaya of "Chloromycetin".

The results of Drs. Smadel and Jackson in eggs and mice are indeed very striking, and appear to me (as to you) to make a field trial imperative; and I cabled to you on 17.11.47 accordingly. If they are bourne out in man the advent of this anti-biotic would constitute a notable advance in the treatment of scrub-typhus. The achievement of any reduction of the mortality-rate and the severity of this disease would diminish the dread in which this disease is held amongst the planting communities in Malaya and adjacent territories; they now fear it much more than they do malaria.

The most significant findings are, I think, in Table 1, relating to the dosage given to mice as late as the 5th, 8th, and 10th days. The average incubation period in man may be taken as 10 days; and the average duration of the ensuing fever to be a further 15 days; so that the period between the day of the mite-bite and the beginning of convalescence (or the intervention of death) is very approximately 25 days. At the dosage of the infecting inoculum used (10^{-5}) the control mice died between the 14th and 18th day after the day of the injection of the virus. The 5th, 8th and 10th day in inoculated mice would therefore correspond very approximately to the 8th, 12, and 16th day after the occurrence of the mite-bite in man.

I emphasize this, since in hospital and estate practice in Malaya it is exceptional for the investigator of scrub-typhus to get access to the patient before the 4th day of fever; most are first seen on the 5th or 6th day of fever; but in a special intensive enquiry such as this would be, it should be possible to reduce that time-lag by at least one day. The reasons for this time-lag are partly that not all cases come immediately to the notice of a physician skilled in the early diagnosis of scrub-typhus, and partly to the fact that the severity of the infection may not become marked (and so suggest scrub-typhus) until the end of the first week, unless an eschar should be present. (An eschar is present in most of the fair-skinned patients, but absent in the dark-skinned, who form the majority of our infections).

The excellent results obtained in mice by injections of the drug on the 8th and 10th days should therefore be assessable in human cases; in exceptional cases those of the 5th day would also be assessable.

During the Japanese war the number of infected areas appear to have increased, due doubtless to factors favouring an increase of the rat population. Within a radius of 20 miles from Kuala Lumpur alone there are 5 persistently infected foci of countryside well-known to us. And many more exist further afield.

The number of cases has also increased; though in less proportion, owing to the present reduced tempo of work in this looted country, and to the scores of thousands of Indian labourers who, forcibly transported by the Japanese to work on the Siam-Burma railway, died there, and have not been replaced. But this reduced tempo of work is a passing phase. Scrub-typhus is, as you know, an occupational disease of the countryside; and as the planting communities return to their former degree of activity, so will the incidence correspondingly increase. I stress this point

since, because of it, it may be necessary for your unit to spend 6 to 12 months in Malaya in order to get 40 cases within their immediate observation. The occurrence of cases is fitful and unpredictable. There will be a steady 3 or 4 accessible cases per month; then perhaps a sudden flare-up, due usually to lalang-clearing in some new area. Thus, 18 months ago, about 300 Jap prisoners were set to work to clear an area some 12 miles from Kuala Lumpur for food cultivation; and amongst a section of them working in one corner of one field about 70 cases of scrub-typhus occurred within a few weeks.

You will agree, I feel sure, that a prolongation by additional few months of the contemplated three months' period of observation would be fully justified in view of the great promise of "Chloromycetin".

One particular point occurs to me about controls. The death-rate in Malaya has usually been about 15 per cent; at the present time it is much the same; certainly it is not less than 10 per cent. Of those that recover, the majority are critically ill about the 10th to 12th day of fever. You may therefore cosider it preferable to treat all or most of the available cases with "Chloromycetin", and rely on pre-war and post-war figures and charts for controls. Such a procedure would avoid a protraction of the enquiry that might prove irksome to your visit. The decision in the matter will, of course, lie entirely with your unit.

I have spoken to the Director of Medical Services on this project, and he also warmly welcomes the visit of your team.

The possibility of the occurrence of small flare-ups of the disease in areas that might be as far as 100 to 150 miles from Kuala Lumpur would make fast road-transport imperative. Cars of the Ford V8 type could probably be put at your disposal by the local Government by arrangement nearer the time of your team's arrival, as the dearth of cars here is slowly yielding to increasing imports. But if your tentative plans should include the bringing of your own cars, so much the better.

As to when the investigation should start, I would suggest that the sooner the better. The disease is not seasonal in Malaya, so that there is no need to await any particular period of the year.

In all details of treatment your team would have a free hand; these and any other such points could be speedily settled once your team is here.

Let me assure you once more than every facility will be afforded by us to further this very promising venture.

Yours sincerely,

/s/ R. Lewthwaite
(R. Lewthwaite)

COPY DIRECTOR.
es

ARMY MEDICAL CENTER **JES/rcl**
Army Medical Department Research and Graduate School
Washington 12, D. C.

MEDEC-ZAMV (Air Mail) 8 December 1947

Dr. R. Lewthwaite, Director
Institute for Medical Research
Kuala Lumpur, Malaya

Dear Doctor Lewthwaite:

We here at the School are delighted with your invitation to study the efficacy of Chloromycetin in the treatment of scrub typhus. We shall be there as soon as arrangements can be made. In the formulation of our plans we shall, of course, depend heavily upon you for advice and suggestions. I hope that you will be as generous in your advice regarding the formation of the plan as you have been in your offer of help to the group after it arrives in Kuala Lumpur.

It is our present tentative plan to employ a small, highly mobile group which can be brought there by air in the early spring. The group would consist of myself, Dr. Theodore E. Woodward, formerly of the U. S. A. Typhus Commission, and Lt. Herbert Ley, M. C., of this Department. I hope that Dr. Cornelius Philip, also formerly of the U. S. A. Typhus Commission and now back at the Rocky Mountain Laboratory, will be able to come with us. With such a staff of three physicians and one entomologist and all with laboratory experience, it should be possible to do the work we have in mind.

I assume that patients with scrub typhus who make up the study group will be under the immediate care of a local physician whether they are hospitalized in Kuala Lumpur or on one of the plantations. We shall be glad to assist in all ways in the care of such patients, but since none of us will be licensed to practice in Malaya, the responsibility for the care of the patients must rest with a licensed physician. It is our hope that alternate patients can be treated (1) in the present manner employed there and (2) with Chloromycetin plus the identical type of hospital care. If the benefits from Chloromycetin are indeed startling in patients with scrub typhus, then perhaps the use of alternate control cases can be abandoned fairly early.

It would appear desirable to keep the study as simple as possible in this initial trial. Thus, clinical observations, temperature records, etc., blood counts and urinalyses together with a few other types of examinations should be sufficient. The more detailed tests which may be done when indicated are blood non-protein nitrogen, blood sugar and one of the simple liver function tests. In addition, it will be desirable to do a number of determinations of blood level of Chloromycetin. This last technique is a bacteriological assay employing inhibition of growth of the Sonne strain of dysentery in fluid media. Equipment for the simple laboratory tests can be flown in without difficulty. If facilities are availablethere for bacteriological work, i.e., for preparation and sterilization of media and for incubation, it would be most helpful. While I know these would be available under ordinary circumstances, I realize that such facilities may be extremely limited at the present time, and therefore ask whether we should bring this equipment.

The diagnosis of scrub typhus in each patient in the study group can be established by isolation of the organism by inoculation of blood into mice and by the development of OX-K agglutinins. While we shall be interested in collecting sera for specific rickettsial tests, it does not seem feasible to attempt to perform them in Malaya. The isolation should require not more than 10 mice for recovery and perhaps one passage of the agent until the rickettsiae can be demonstrated in smears. Is it possible to obtain locally such numbers of mice for this purpose, or would it be desirable to bring a stock and arrange for additional shipments during the study? I think it important that attempts at isolation be made regularly, particularly, since Woodward has recently found that patients with spotted fever who are vigorously treated with para-aminobenzoic acid and recover promptly, show a poor antibody response.

Should we consider bringing a small, light table centrifuge, using 110 volt, 60 cycle current?

I am worried about transportation facilities. It would appear impossible to bring an automobile. Do you think it worthwhile considering transporting a motorcycle? Further, would a light liaison plane be of sufficient value for us to go through the difficult process of trying to have one assigned to the group?

A number of studies are now in progress to extend observations on the chemoprophylactic effect of Chloromycetin on scrub typhus infections in mice. If these continue to give promising results, it might be worthwhile to consider a small field trial in human beings, if conditions were suitable. Are the endemically infected areas sufficiently well defined so that one can predict with some accuracy that the group sent in to clean up the area is likely to become infected? If such predictions are possible, is it the custom to clean the area or to abandon it? If cleaning is done in spite of scrub typhus, it might be possible to obtain information on the chemoprophylactic effect without much delay.

With very best wishes,

JOSEPH E. SMADEL, M.D.
Scientific Director
Department of Virus and
Rickettsial Diseases

During World War II, it was my privilege to have met Doctor Smadel first at the Army Medical School (WRAIR). Later we cemented a firm and lasting friendship at Naples, Italy during the outbreak of louse-borne typhus in 1944-45. Here, for the first time, an epidemic of louse typhus was stopped in its tracks because of the remarkable effectiveness of the anti-lousocidal powder, DDT. Joe had come to the Italian Theater from England, on assignment, to observe the various control measures which were being applied to control the epidemic. Following the war, it was my decision to enter private practice of medicine in Baltimore with a minor faculty teaching appointment at the University of Maryland School of Medicine and Hospital. To escape the rigors of medical practice and resume personal interests in the rickettsial diseases, it was my routine to travel to WRAIR every Thursday to work in collaboration with Joe and his

capable associates. We exchanged ideas about the rickettsioses and the experience served me well as postgraduate educational experience. Following is an anecdotal account of those events which describe the first Medical Mission to Kuala Lumpur. This was the forerunner of subsequent, long-term developments in this far eastern tropical country.

Joe asked me to join the group and selected the research team shown in the figure 2 — Herb Ley, Scientific Laboratory Assistant to Joe (staff member at WRAIR), Cornelius (Neil) Philip (Deputy Director, Public Health Service Laboratory, Hamilton, Montana), Robert (Bob) Traub (staff entomologist, WRAIR), and myself as clinician. The original contract, funded by the U. S. Medical Research and Development Command under the aegis of the Commission on Immunization of the Armed Forces Epidemiological Board, was awarded to the University of Maryland School of Medicine. Later, during a discussion of a meeting of the Armed Forces Epidemiological Board, Dr. Stanhope Bayne-Jones (B-J) quipped that this contract "was conceived in inequity and executed in sin" and retorted promptly that "it got things done."

Figure 2. U.S.A. Scrub Typhus Team, shown at IMR, Kuala, Lumpur, Malaya, April, 1948. From left: Traub, Woodward, Smadel (Team Leader), Philip, Ley.

Travel to Kuala Lumpur

A special military transport plane carried the team and essential equipment, including refrigerators, incubators and two jeeps. Several spicy incidents relieved the monotony of the long journey across the Pacific to Singapore. Joe held a royal straight flush in diamonds at the Hamilton Air Force Terminal. We immediately froze the deck. Later, in Kwajelein, a near rupture of the small unit almost occurred. The island was a highly restricted area because of pending nuclear testing. The small group was cautioned by the Traffic Officer to exit the plane, go directly to a small holding shack and remain there until notified to board the plane. One of the team members, in spite of careful instructions, failed to make the passenger count at time of departure. The air force pilot, a Lieutenant Colonel, was irate and Joe was livid. The temperature inside the cabin exceeded 110 degrees. It was increased by 30 degrees with Joe's crisp verbage when our wandering scientist returned with a new species of grasshopper taken from a restricted red area across the landing strip.

Doctor Lewthwaite met the plane in Singapore on Saturday, March 13, 1948. The Sunday holiday precluded removal of the jeeps and other heavy equipment by airport personnel. Steaming and undaunted, Joe was bursting for action and practically built a makeshift block and tackle for the purpose. We immediately motored in our two jeeps through the green Malayan Rain Forest with its rubber plantations and isolated tin mines to the Selangor capital of Kuala Lumpur.

Figure 3. Dr. R. Lewthwaite, Director
Institute for Medical Research, Kuala Lumpur.

Initial Studies: Scrub Typhus Patients Respond Dramatically

Unbelievably, before a change of clothes, Doctor Lewthwaite took us to the bedside of a young Malayan soldier named Mohammed Osman who was in the general civilian hospital adjacent to the IMR. Osman had acquired his illness near the air strip in K.L. The history revealed headache, prostration and fever of five days, and, upon examination, a tell-tale eschar in the right axilla with adjacent adenopathy. After examination, blood was taken for the routine laboratory evaluation of hemoglobin, leukocyte count, acute phase serum for the Weil-Felix OX K reaction and injection of mice intraperitoneally for rickettsial isolation. A picture was taken of patient Osman in the hot midday sun in which his eschar is visible.

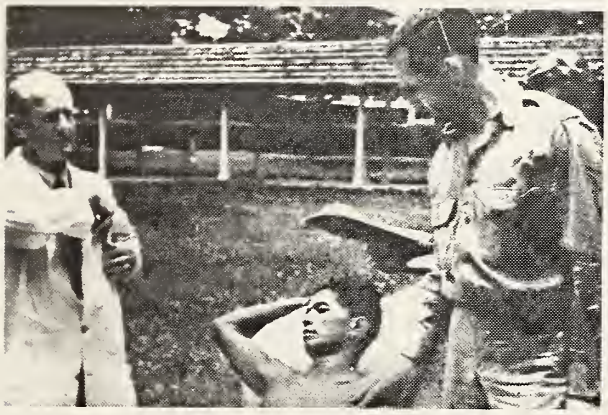

Figure 4. Scrub Typhus Patient, M. Osman, showing eschar in left axilla. R. Lewthwaite (left) and T. E. Woodward.

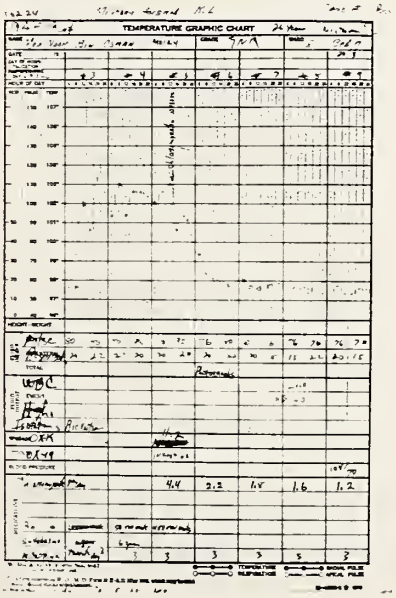

Figure 5. Temperature chart of patient, M. Osman. Note prompt febrile response about 24 hours after initiating Chloromycetin response.

A loading oral dose of 2.0 grams of Chloromycetin using large 250 mgm tablets was given with a subsequent schedule of one tablet every two hours until the twelfth day of illness. Joe had surmised that specific therapy should continue until an immune response had occurred indicated by emergence of Proteus OX K agglutinins which appeared usually late in the second febrile week. By noon the next day, Osman was noticeably improved, less toxic in appearance, headache gone and afebrile twenty-four hours after beginning tretment. Subsequently, the diagnosis of scrub typhus was confirmed by isolation of rickettsia in mice and rise in titer of Proteus OX K agglutinins. Recovery was prompt and complete without relapse.

The second patient was Corporal Bebbington, of His Majesty's Forces, who was treated in the military hospital. Initially quite ill, he responded promptly within thirty hours and did not relapse.

A steady flow of subject typhus patients in the civilian and military hospitals of K.L., in the nearby rubber estates, medical wards and surrounding villages insured an adequate clinical trial. Among these ill patients was a hardy group of Gurkha soldiers who were treated in the military hospital. There was no simultaneously untreated control series. Patients thought to have scrub typhus on clinical grounds were selected and treated consecutively. Of the first forty patients, thirty were confirmed as having scrub typhus. The additional ten included two with murine typhus, two malaria, one with blackwater fever, two leptospirosis, two with typhoid to be described later, and two with GKW (God knows what). This represented a clinical diagnostic batting average of 75 per cent.

We experienced a striking example of the rapid spread of news. Doctor Lewthwaite received a telephone call from Dr. Stanley Pavillard, a prominent Singapore physician, whose patient, a banker, was desperately ill with scrub typhus in its late

stages. News reached Singapore via a British Army Officer traveling by train from K.L. Familiar with the recovery of Corporal Bebbington, he related the miraculous event to another passenger who was visiting in the patient's home. They, in turn, called the IMR and asked for help. Doctor Lewthwaite and I coerced Joe, in spite of his protestations, to broaden the area of patient selection and treat the banker in view of diplomatic amenities, which included the fact that we were guests in Malaya. The afternoon plane from Ipoh, which took me to Singapore, was strewn with flowers and carried an urn containing a portion of the ashes of Mahatma Ghandi. Approximately thirty thousand overly excited native Hindus met that plane. Doctor Pavillard cleverly extracted me from the mob using the baggage exit of the plane and drove directly to the hospital. In spite of the patient's domineering wife, who was a former nurse, and the patient's impending vascular collapse, delirium and a purplish exanthem, the banker, case no. 9 in the series, recovered. This feat established beyond doubt that the antibiotic was remarkably effective at all stages.

Very early in the trials, Howard Florey (later, Sir), who was en route London from Australia, stopped in K.L. to observe the clinical trials. After personally witnessing the twenty-four hour recovery of a scrub typhus patient and observing the clinical responses of the first few cases treated which had been displayed graphically, Sir Howard remarked, "I'll buy it, you don't need statistical evidence."

Joe directed a tight laboratory program. Initial and convalescent blood specimens, daily temperature and pulse responses, and an audit of Chloromycetin tablets were all duly recorded. Once he observed a laboratory associate pouring serum from a tube of clotted blood into another tube. A quick retort, "Chum, hereafter the tube will be centrifuged and the serum pipetted." This admonition with additional epithets, ended this practice.

Soon, it was clear that Chloromycetin cured scrub typhus patients promptly. Based on this confidence, the therapeutic regimen was reduced to one day's treatment and even one 3.0 gram dose. All led to recovery without relapse provided treatment was initiated not earlier than the fifth day of illness. Relapses were later encountered in patients who were treated prior to the fifth febrile day. These clinical results provided a basis for understanding the difficulties encountered in the subsequent chemoprophylactic field trials.

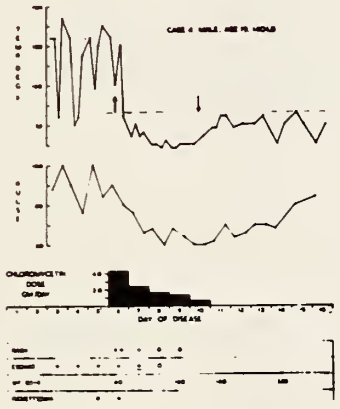

Figure 6. Scrub Typhus (Composite)
(a) Chloramphenicol initiated on 6th day of illness and continued until 11th day. No relapse.

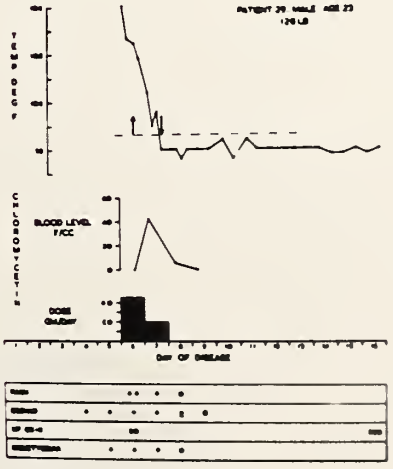

Figure 6. Scrub Typhus (Composite)
(b) Chloramphenicol treatment given for only 24 hours beginning on 6th day of illness. No relapse.

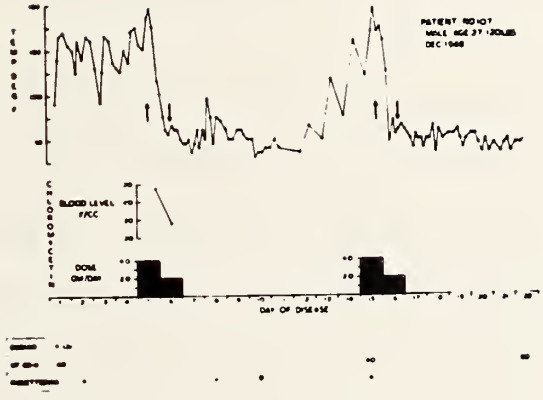

Figure 6. Scrub Typhus (Composite)
(c) Chloramphenicol treatment initiated on 5th day of illness. Note presence of rickettsiemia on 8th day while not receiving antibiotic. Relapse occurred with prompt response on retreatment.

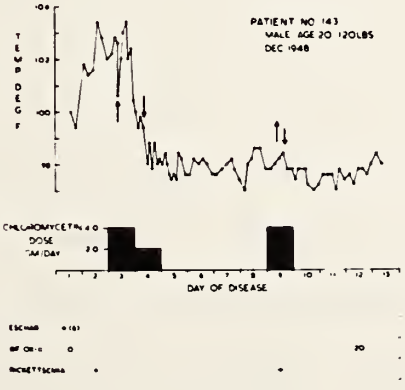

Figure 6. Scrub Typhus (Composite)
(d) Interrupted chloramphenicol treatment regimen. Note prompt response to initiat treatment on 3rd day of illness and one day treatment with chloramphenicol on 9th day when rickettsiemia was present. Febrile relapse prevented.

Typhoid Patients Respond to Chloramphenicol

On Saturday night, April 3, 1948, we were informed of two new febrile patients, numbers 17 and 18 in the initial series, who were transported from a rubber plantation ordinarily reliable as a source of scrub typhus patients. By candlelight, the brief clinical history and examination were completed. Specimens were obtained for laboratory evaluation. Both patients were toxic and neither had an eschar. In twenty-four hours, one patient was improved dramatically in keeping with the prior therapeutic experience in scrub typhus. The second patient, number 18, was unchanged; he appeared toxic, apathetic with abdominal distress and diarrhea. Enteric fever was suspected. Since blood cultures were not included in our routine, an attempt was made to retrieve tyhoid bacilli from the peritoneal exudate of mice inoculated with blood. The smear was not confirmatory but cultures of peritoneal exudate, and other specimens of the patient's blood, yielded organisms. Therapy with Chloromycetin was continued because, at the bedside he seemed to be a shade better. Joe was annoyed that precious Chloromycetin tablets were being expended on a non-mission oriented problem, but he relented. Within two days, clinical improvement was apparent based on bedside findings; defervescence occurred in about three days. Treatment was discontinued after the patient had five days of normal temperature; eight days later, he greeted us with a full-blown relapse and a toxic psychosis. The patient's relapse responded to additional therapy. Incidentally, his name was Mohammed Ali.

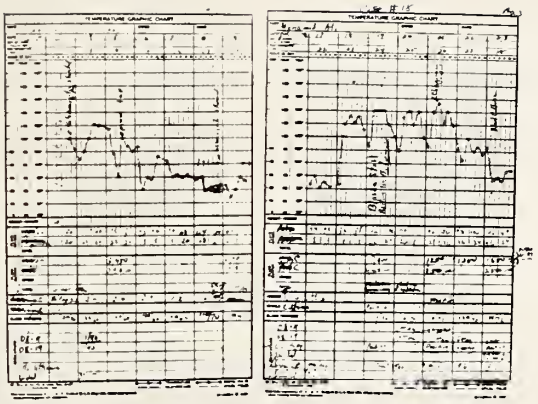

Figure 7. Typhoid Fever. Graphic record and pertinent findings of first patient successfully treated with Chloromycetin in Kuala Lumpur in 1948. Patient developed a febrile relapse (8 days) after stopping Chloromycetin). Retreatment led to prompt response.

The second selected typhoid patient responded in less that four days and did not relapse. There was trouble ahead which caused a little team agitation and concern. Among the ten treated typhoid patients, two relapsed, one became temporarily psychotic, another developed gross hemorrhage which required transfusion, and one suffered intestinal perforation with peritonitis and shock. Concerning this very ill patient, whom I selected for treatment on the seventeenth day, Joe remarked, "Why start treatment on such an ill patient, do you want to ruin the series?" My retort that we ought to determine the true efficacy of Chloromycetin in typhoid provided little solace to the conversation. This patient's intestine perforated two days later; yet, he and all other patients recovered. In spite of this inauspicious beginning, we were convinced of the therapeutic benefit in these seriously ill typhoid patients and published the results based on ten typhoid patients. (Ref.)

After the obvious dramatic therapeutic response in scrub typhus patients, Joe directed the field prophylactic studies to determine if the disease could be prevented with Chloromycetin after natural exposure. American, English and Malayan volunteers were purposely exposed by sitting eight hours daily for ten days in a mite-ridden typhus infested area.

The Straits Times

MALAYA'S LEADING NEWSPAPER ESTABLISHED 1845

SINGAPORE, TUESDAY, MAY 6, 1941

30 Men Wanted For Scrub Typhus Tests

From Our Staff Correspondent

KUALA LUMPUR, Monday

AMERICAN and British scientists who have been investigating scrub typhus in Malaya, are appealing for 30 volunteers to participate in a field experiment among Kuala Lumpur

The results of the investigation," says an official statement, "may well prove that scrub typhus can now be prevented by prophylactic treatment just as can Malaria.

The volunteers will be required for 10 days in the field and on conclusion of their duties will be specially examined about

"Share Experience"

The experiment will take place during the next few weeks and the scientists in charge of the volunteers from the general public to share the experience with them.

Volunteers are asked to notify the Director of the Institute for Medical Research at once by letter or telephone (K.L. 3081) by 12 noon today.

Request

Figure 8. Newspaper request for volunteers to participate in a chemoprophylactic field trial to evaluate efficacy of Chloromycetin.

Scrub Typhus: Chemoprophylactic Field Trial

Many of the scrub typhus patients whom we treated in the initial series were infected originally at the Seaport Rubber Estate outside K.L. Also, the dresser, named Pillai, who assisted me in many ways, had given the valuable information that a Japanese unit which had bivouacked there during the occupation had experienced a very high attack rate of scrub typhus. Shown in the photograph is the jungle setting where the chemoprophylaxis trials were conducted. Bob Traub, Cornelius Philip, Ralph Audy and

his team had pinpointed the small isolated areas (typhus islands) which contained large numbers of infected mites.

Figure 9. Seaport Rubber Estate outside Kuala Lumpur. Actual site of successful chemoprophylactic field trials in 1948. Notice volunteers under umbrellas.

These human field trials, which extended for several years, revealed that clinical scrub typhus infection could be suppressed by administering the antibiotic at intervals once every four or five days for about seven weeks. Shorter, intermittent regimens resulted in rickettsemia and clinical illness. Giving Chloromycetin simultaneously, at the first day of infection, daily for twenty-eight days merely extended the incubation period; classic illness occurred seven days after stopping the drug.

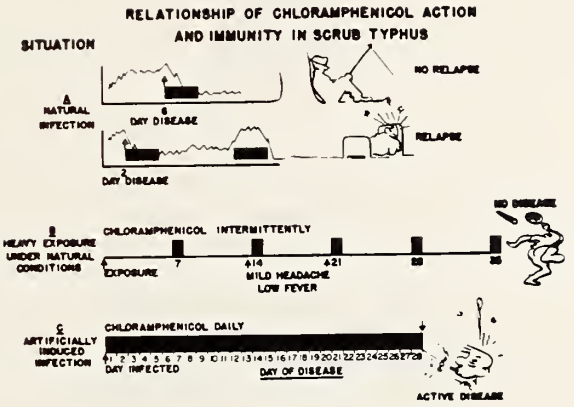

Figure 10. Summary graphs of chemoprophylactic field trial which showed that scrub typhus could be prevented by giving Chloromycetin intermittently once every 5 days for 7 doses. This composite cartoon represents a compilation of data conducted from 1948 to 1952.

The therapeutic findings in patients and results of the field trials in volunteers demonstrated the rickettsiostatic properties of Chloromycetin and established that resistance to infection bore a relationship to a sustained or sufficient intermittent antigenic stimulus. The field trials effectively demonstrated the immunologic relationships between host, microbe and antibiotic and provide essential guidelines of chemoprophylaxis based on active immunization. Joe Smadel and Neil Philip, as non-immunes, developed severe attacks of typhus and recovered fully with Chloromycetin treatment. Charles Wisseman, Bennett Elisberg, Bob Traub and others were active contributors to the later studies.

Citation

For meritarious service rendered in the cause of medicine, science, and humanity.

participated as a volunteer in field investigations of scrub typhus carried an in Kuala Lumpur during 1948. His efforts contributed materially to advancements in the methods for the preventian and cantrol af this farmerly dreaded disease.

(Joseph E. Smadel)
U. S. Army Scrub Typhus
Research Unit.

(R. Lewthwaite)
Director.
Institute for Medical Research.
Kuala Lumpur.

Figure 11. Copy of Certificate awarded to each volunteer who participated in the scrub typhus field trials.

Each volunteer who participated in the field trial was given an appropriately worded certificate which designated his contribution. A number of press releases highlighted the group's activities.

VICTORY!

Figure 12. Cartoonist impression after first successful clinical trial of Chloromycetin treatment of scrub typhus patients in Kuala Lumpur, Malaya, in 1948. Malaya Mail, 1948. From left: Woodward, Philip, Traub, Ley, Smadel.

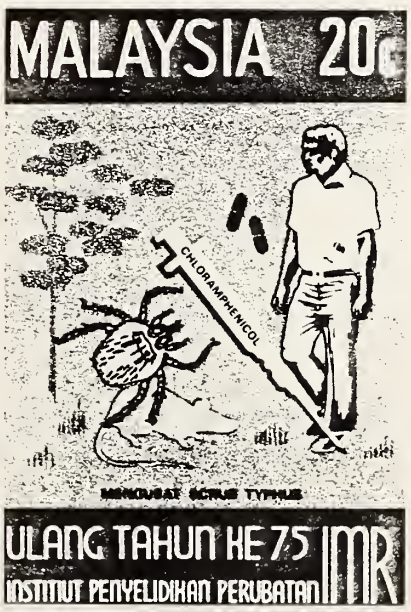

Figure 13. Front page of a Malay Magazine which highlighted the Team activities.

Close of First Visit to K.L.

One night Joe borrowed the "clinical" jeep which I alone used. He soon ran out of gas and after returning to the billet by foot, promptly awakened me for a lecture in automotive toilette. The breakfast atmosphere was rather chilly. That very day, at noon, after morning rounds, I parked my jeep in front of a Chinese cabinet maker's shop on Ampang Road (Wai Fong) to check progress of a teakwood chest which had been ordered. The front door closed lightly and Joe entered and made a kind remark about my handsome chest. With great courage, he remarked, "I just ran out of gas with the other jeep, will you please push me back to the IMR?" Perfect timing!

Following is a list of those publications which accrued as a direct result of those studies of Chloromycetin (chloramphenicol) which were iniated in 1948.

Smadel, J. E., Woodward, T. E., Ley, H. L., Jr., Philip, C. B., Traub, R., Lewthwaite, R. and Savoor, S. R.: Chloromycetin in the treatment of scrub typhus. Science **108:** 160-161, 1948.

Woodward, T. E., Smadel, J. E., Ley, H. L., Jr., Green, R. and Mankikar, D. S.: Preliminary report on the beneficial effect of Chloromycetin in the treatment of typhoid fever. Ann. Int. Med. **29:** 131-134, 1948.

Pincoffs, M. C., Guy, E. G., Lister, L. M., Woodward, T. E. and Smadel, J. E.: The treatment of RMSF with Chloromycetin. Ann. Int. Med. 656-663, 1948.

Philip, C. B., Traub, R. and Smadel, J. E.: Chloramphenicol (Chloromycetin) in the chemoprophylaxis of scrub typhus (tsutsugamushi disease). I. Epidemiological observations on hyperendemic areas of scrub typhus in Malaya. Am. J. Hyg. **50:** 63-74, 1949.

Smadel, J. E., Woodward, T. E., Ley, H. L., Jr. and Lewthwaite, R.: Chloramphenicol (Chloromycetin) in the treatment of tsutsugamushi disease (scrub typhus). J. Clin. Invest. **XXVIII:** 1196-1215, 1949.

Smadel, J. E., Woodward, T. E. and Bailey, C. A.: Relation of relapses in typhoid to duration of chloramphenicol therapy. JAMA **141:** 129, 1949.

The initial venture to Kuala Lumpur ended in June, 1948, with a total cost to the American government of less that $50,000. This imaginative medical mission to Malaya conceived by Joe Smadel was the forerunner of continued scientific collaboration between scientists of the IMR in Kuala Lumpur, WRAIR and Maryland. The new therapeutic, epidemiologic and preventative techniques which resulted from this cooperative international program are a fitting memorial to a remarkably stimulating, vigorous and talented medical scientist.

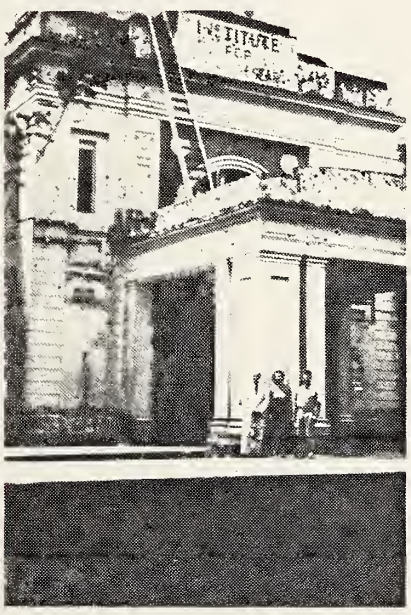

Figure 14. Photograph of Institute for Medical Research (IMR), Kuala Lumpur, Malaya, March, 1948. The Second Typhus Team performed its laboratory work on second floor of the Institute. Shown are: Dr. R. Lewthwaite, Director, and Dr. and Mrs. Ralph Audy (British entomologist).

This inaugural cooperative medical research experience in Kuala Lumpur at the Institute for Medical Research (IMR) opened the door for development of the United States Army Medical Research Unit which has a continued record of achievement under

sponsorship of WRAIR and the U. S. Army Medical Department Research and Development Command.

CHOLERA PROGRAM IN BANGKOK, THAILAND

Introduction and Early Events

Cholera has ravaged the Asian subcontinent for centuries, always present in India and Pakistan with a heavy toll in numbers of cases and deaths. Cholera has periodically spread to adjacent countries and elsewhere. This occurred in Thailand, Hong Kong, the Philippines and throughout the East, beginning in 1958. Although Thailand had experienced prior epidemics, there was an apparent absence of observed cases there from 1950 to May, 1958. (Ref.)

Prompted by this major threat, the Thai Government invited the U. S. Naval Medical Research Unit No. 2 (NAMRU-2) to conduct studies on patients suffering from cholera in Bangkok. The work began in 1958 and extended through 1959, until the spring of 1960. During 1959, a combined team consisting of scientists from WRAIR and NIH worked collaboratively in Bangkok with NAMRU-2 and Thai investigators, epidemiologists and allied health personnel. Dr. James H. Shannon, Director of the N.I.H. was consulted by the Department of State in connection with a plan to develop a health program under auspices of the Southeast Asia Treaty Organization (SEATO) to help the people of southeast Asia. Doctor Shannon asked his Deputy Director, Joseph E. Smadel, to recommend a program with starting funds available in the amount of $400,000. which were derived from the International Cooperative Administration (ICA). Joe convened a small working group consisting of Kenneth Goodner, Professor of Microbiology at Jefferson Medical College, John H. Dingle, Professor of Preventive

Preventive Medicine at Case Western Reserve, Dr. Colin M. MacLeod, Professor of Experimental Medicine, University of Pennsylvania School of Medicine, Colonel Richard Mason, Commandant, WRAIR, Theodore E. Woodward, Professor of Medicine, University of Maryland School Medicine.

Team Visit to the Far East

Asiatic cholera was then significant as a disease which afflicted south Asian people and caused an unprecedented number of deaths and morbidity. In order to assess the magnitude of the problem and develop a better understanding of those facts, known and unknown, about the disease, the group visited leading centers in the Far East and in Asia.

Figure 15. Kenneth Goodner (left) and Joseph E. Smadel, major organizers of the cholera program, viewing the East Portico of the Parthenon in Athens. Picture taken by author during a one day stopover in Greece enroute the States from Dacca in 1960.

Figure 16. Japanese scientists with first U.S.A. cholera group taken at the National Institutes of Health. Taken in Tokyo, September, 1959.

Tokyo was the first site visited where a series of conferences and workshops were held at the National Institutes of Health, Tokyo, and the Kitasato Institute. Taipei proved to be a most important site visit because Capt. Robert Phillips, Commandant of NAMRU-2 and his staff were conducting landmark, physiologic studies of the various abnormalities present in cholera, as well as therapy based on fluid replacement. Much helpful information was gleaned in Taipei regarding diagnosis, pathogenesis and control of cholera.

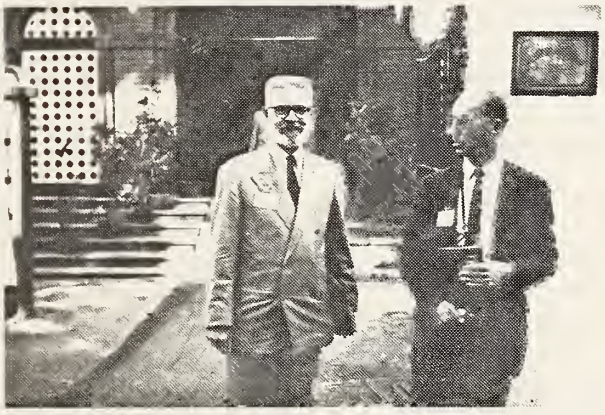

Figure 17. Robert A. Phillips (left), Colin MacLeod, Dacca, December, 1960.

At this time, Manila was experiencing an outbreak of El Tor type of cholera which was a controversial matter regarding the significance of its pathogenicity. Goodner had always insisted that the strain was pathogenic and virulent. Philippine authorities had taken a different view until the epidemic reached alarming proportions. Laboratory and public health authorities in the Philippines, as well as faculty members of the University of Philippines were anxious to have a research center for the study of cholera located in Manila. Hong Kong was visited with the sole purpose of conferring with authorities there to learn of the preventive measures which had been effectively applied to arrest cholera in this important far eastern port. At all of the locations visited, Ken Goodner collected strains of Vibrios from laboratories, from ponds and gutters which he transported back to Philadelphia for future study.

If the group previously had a preferred site in mind to place a research center, Bangkok would have been the sentimental favorite. This was because research facilities were readily available. The professional attitude of scientists there was most affable and cholera patients were prevalent in large numbers but only periodically.During this visit, there was exchange of valuable information and friendly visits to the Thai Armed Forces Institute of Pathology.

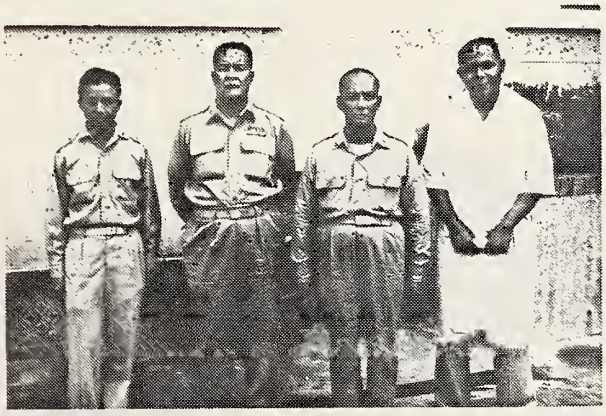

Figure 18. Group of Thai pathologists, taken at Thai Armed Forces Institute of Pathology, Bangkok, October, 1959. From left: Samnieng Busapavanich, Chief, Bacteriology; Thanon Uppathampanonda, Surgeon General, Thai Army; Phung Phintuyothin, Pathologist; Charas Thephusdin.

Ken Goodner was a key team member for many reasons. He was very well informed about the bacteriologic and immunologic aspects of cholera. Also, his friend, Dr. Luang Binbakya Bidyabhed (Pyn), an alumnus of Jefferson Medical College, and Thailand's leading radiologist, was Undersecretary of State for Health. Pyn was one of Thailand's recognized statesmen for health. He had previously arranged a brief reception

for the group with His Majesty, King Bhumibol Adulyadej. The audience, held in a magnificient reception hall, had been scheduled originally to last fifteen minutes; it lasted one and one-half hours. Joe Smadel, as the leader of our small medical group, according to protocol was expected to carry on the conversation with the young king. Joe kept stressing the need for research and King Bhumibol answered several times, "Yes, Doctor Smadel, but how will the research help my people?"

Figure 19. Audience with His Majesty, King Bhumibol Adulyadej, taken at the Palace, October, 1959. Showing U.S.A. cholera group. From left: Richard Mason, Theodore E. Woodward, Dr. Pyn, John Dingle, Colin MacLeod, Kenneth Goodner, Joseph E. Smadel.

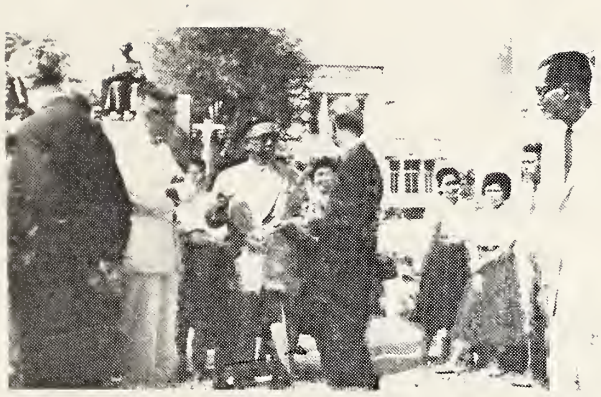

Figure 20. Bangkok, October 1959. From left: Charles Richards, M.D., ICA; Dr. Luang Binbakya Bidyabhed (Pyn); Colin M. MacLeod, M.D. Taken at the statue of Prince Sankla, Siriraj University.

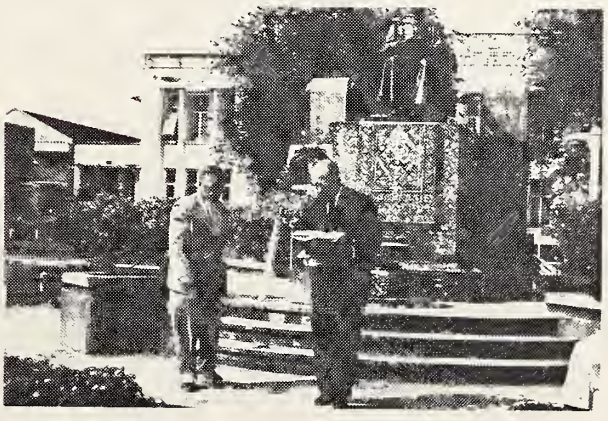

Figure 21. Bangkok, 1959. Statue of Prince Sankla, Siriraj University. Left: Dr. Luang Binbakya Bidyabhed (Pyn), Dr. Kenneth Goodner.

In spite of the very favorable scientific and friendly atmosphere in Bangkok, the group had some reservation regarding the decision to place a permanent cholera research center there. This was simply because it was felt that Asiatic cholera would not remain prevalent in Bangkok or in Thailand because of the very energetic and effective control measures which had been put into action. Nevertheless, a Thailand Cholera Research Laboratory was soon established in Bangkok on the premises of the Thai Armed Forces Institute of Pathology.

Although India was not a member of the Southeast Asia Treaty Organization, the group next visited New Delhi. Here, C. G. Pandit, Director, Indian Medical Research Council, members of the Health Ministry, and faculty members of the All India Medical School provided much valuable data on the epidemiologic patterns of cholera in India. Next, in Calcutta, many cholera patients were observed in two large metropolitan hospitals; cholera experts there provided important information on the methods of laboratory diagnosis and treatment.

In Dacca, everything seemed ideal for placement of a Cholera Research Laboratory. Cholera patients were very accessible and available in droves every year. The disease seemed to be permanently established in this population dense country which, during wet seasons, was partially inundated in water. Health authorities were anxious and most enthusiastic in their desire to establish a research center there. An entire wing of the Public Health Institute was made available for laboratory work, administrative offices and for the clinical investigation of cholera. Here the SEATO Cholera Research Center found a permanent home. With these decisions consummated, including agreed plans for research centers in Bangkok and Dacca, the group felt that the site visits had been productive and would prove successful.

Figure 22. James Shannon, M.D. (left), Robert A. Phillips, M.D., U.S.N. Taken in Dacca, December, 1960.

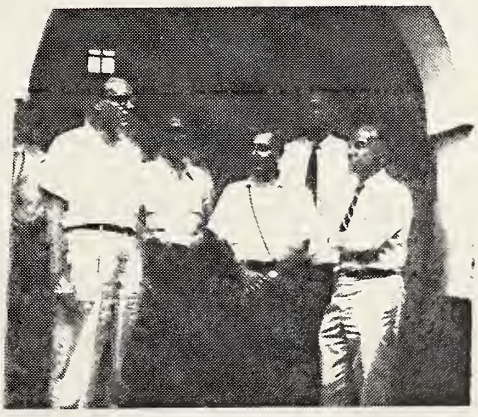

Figure 23. Photograph taken in Dacca, 1974. From left: Clifford Pease, Abram Benenson, Eugene Gangarosa, Charles Carpenter, Robert Berliner.

BEGINNINGS OF AFRIMS

Earlier Work on Cholera in Thailand

The Thailand Southeast Asia Treaty Organization (SEATO) Cholera Research Laboratory had the helpful advantage of prior work on cholera performed by Thai and United States personnel in 1958-1959, when the disease was a serious problem in Thailand. The Royal Thai Government had invited several groups of civilian and military scientists to work on a short-term basis in Bangkok and Dhonburi. These initial studies under the direction of Capt. Robert A. Phillips (Commandant NAMRU-2) embraced the biochemical, physical and tissue alterations which were said to occur in cholera patients. This work included isolation and characterization of the causative vibrios along with ecologic and epidemiologic observations. The SEATO Council of Ministers soon recognized the importance of the cholera problem in Asia.

Decision to Establish a SEATO Cholera Research Laboratory in Bangkok

It was in this setting that the Council, during its fifth meeting in 1959, and in May, 1959, exchanged notes with the United States government. This action culminated in the plan to establish a cholera research project. The International Cooperative Administration (ICA) made $400,000. available for the project and assigned direction to the United States National Institutes of Health. Dr. Joseph E. Smadel was appointed Chairman of the NIH Advisory Committee on Cholera and with Dr. James Shannon selected the other committee members.

Based on its survey and productive discussions which were endorsed unanimously by everyone concerned, the advisory team made the following recommendations.

Report of Cholera Research Advisory Team (Draft 11/2/59)

Appendix IV

Organizational Plan for Cholera Research in Bangkok

The collaborative efforts of Thai and American investigators in their studies on cholera in 1958 and 1959 have produced significant new knowledge regarding the pathogenesis, epidemiology, treatment and control of this disease. Equally important for future plans, the work of the last two years has established friendly relationships between the U. S. group and the Thai authorities as a genuine interest in continuing the joint studies. Because of these developments, the plan outlined below is given in brief form with full confidence that details can be negotiated without difficulty.

It is proposed:

(1) That the Thailand-SEATO Cholera Research Laboratory be established in Bangkok before the end of the calendar year 1959.

(2) That it be located at the Army Institute of Pathology in space similar to that made available in March 1959 to the visiting American group.

(3) That the Thailand-SEATO Cholera Research Laboratory be responsible in Thailand for Administrative supervision to the Under Secretary of State for Public Health of Thailand who will serve as Director-General of the Laboratory. That it be operated by an Executive Director who will be responsible for technical supervision to the Director, National Institutes of Health.

(4) That the Executive Director, who will be an American scientist, will work closely with the staff of the American Embassy and USOM/Thailand in Bangkok. USOM/Thailand will, among other things, provide assistance in the transfer to the Thailand SEATO Cholera Research Laboratory of funds from the SEATO Cholera Research Account, held under the jurisdiction of the NIH, and of such other funds as

may become available.

(5) In planning and carrying out investigations in Thailand, the Executive Director will receive assistance and overland technical guidance from the Committee on Cholera Research which is to be established by the Director, NIH, to advise him on the operations of the SEATO cholera research program.

(6) That the Thailand-SEATO Laboratory will receive under its aegis visiting investigators and research teams who proposed studies on cholera are acceptable to the Laboratory and the Committee on Cholera Research, and whose members are acceptable to the Thai Government.

(7) That the Thai Ministry of Health will use its good offices to assist the Laboratory in arranging for studies which may be undertaken by its staff, including visiting scientists, in collaboration with the Thai investigators and institutions.

Organization of the Laboratory

The Thai SEATO Cholera Research Laboratory was conceived as a multi service cooperative enterprise undertaken and implemented through the materiel help and goodwill of the governments of Thailand and the United States. Australia made certain items of essential equipment available. These member countries of SEATO, through their willing cooperation and generosity, included donation of equipment and supplies which allowed the yearling laboratory to function on an unusually low budget. From its inception, it was acknowledged that the Thai SEATO Cholera Research Laboratory Project would be temporary for which reason investigative projects were initiated which had a reasonable chance of success.

The laboratory occupied approximately two-thirds of the right wing of the third floor of the Royal Thai Institute of Pathology. Four rooms were used for office, storage, bacteriologic work and special projects. Other space was used on a shared basis with the Department of Bacteriology of the Institute for serologic studies media rooms and sterilization. Later, a special electric meter was installed for this block, gas was delivered in bottles, water was drawn from the common laboratory pipeline and air conditioning for all essential rooms was furnished by the United States Operations Mission (USOM). The Thai Army provided janitorial and security services.

Also, the Thai government provided cholera project personnel which included epidemiologists, dietitians, public health nurse, equipment supplies and services, as well as additional space at the Chulalongkorn Hospital, Bangkok. The Thai government assigned personnel from the Ministry of Public Health, the Chulalongkorn Hospital, the School of Public Health and the Royal Thai Armed Forces to work with the project.

From the United States came personnel, equipment supplies, travel funds, per diem payments and funds for office expenses. Essential supporting funds were derived from ICA arranged through USOM in Bangkok and from the Research and Development Command of the Office of the Surgeon General of the United States Army and the Walter Reed Army Institute of Research (WRAIR), Washington, D. C. Expendable items such as diagnostic sera and reagents were contributed by WRAIR, the United States Navy Medical Research Unit No. 2 (NAMRU-2), Taipei, Formosa, from the 406th General Medical Laboratory and the Sixth U. S. Army Laboratory, Japan. Contributions in kind came from NIH, Bethesda, and WRAIR. Valuable cholera typing sera were provided by the Department of Microbiology of the Jefferson Medical School. The government of Australia contributed an autoclave for the laboratory. Many medical

journals were given by the Philippine government. Siriraj University in Bangkok provided valuable laboratory services. Very helpful support for the identification and characterization of vibrios and other bacterial species was derived from the Indian Institute of Biochemistry and Medical Research, Calcutta, NIH (U.S.A.), WRAIR (USA), and the Sixth U. S. Army Laboratory. These contributions made the laboratory a remarkable cooperative enterprise.

Equally remarkable in spite of its frugal budget was the record of achievement of this small pioneering laboratory. During its year of work, approximately sixteen million dollars came from the ICA as a dollar contribution. Additional ICA/USOM funds supported the work of the NAMRU-2 unit which studied the physiologic abnormalities of Asiatic cholera under the general direction of Capt. Robert A. Phillips, U.S.N., Commander. WRAIR secunded several medical officers (Gangarosa, Beisel, Halstead) to work with the NAMRU-2 unit for evaluation of the pathologic intestinal changes in cholera patients; Robert Gordon was assigned from the National Institutes of Health.

Dr. Amara Chantrapanonda, Chairman of the Department of Nutrition of the School of Public Health, Bangkok, was aided through a grant from the ICA/USOM.

The Royal Thai Army Institute of Pathology's contribution to the project amounted to approximately $9,000. Lumping the various scientific and administrative activities, the United States contributed $30,259.34 to the Thai Cholera Research Laboratory during its tenure of one year and $14,395.18 for non-expendable items. Perhaps there are better examples of more frugal expenditures and the subsequent significant scientific contributions; the writer is not aware of such.

Published Work of Thailand SEATO Research Laboratory

Following is a tabulation of the list of scientific papers published by personnel of the Thai Cholera Research Laboratory (SEATO) and the names of the contributors during its short tenure. (Final Report, Thailand SEATO Research Laboratory, Bangkok, Thailand, November, 1959 to December, 1960. Printed by Sivaphorn Limited Partnership, 74501 Rajjataphan, Makkasan Circle, Bangkok, Thailand.)

Notes on the Isolation and Evaluation of Vibrios in Thailand, by Oscar Felsenfeld, Samnieng Buspavanich, Eugene J. Blair and Chathong Tua.

Epidemiologic and Bacteriologic Observations on Cholera in Bangkok and Dhonburi, November 1959 to July 1960, by Francis M. Morgan, Banyong Thavaramara, Samarn Nanthavanij, Samnieng Buspavanich and Oscar Felsenfeld.

An Outbreak of Diarrhea in which El Tor Vibrios Were Implicated, by Oscar Felsenfeld, Samnieng Buspavanich and Samarn Nanthafanij.

Epidemiologic and Clinical Observations during the Ubol Epidemic, by Suchati Chetansen, Francis M. Morgan and Banyong Thavaramara.

Distribution of Non-Agglutinable Vibrios (NAG) in Thailand during the Year 1960, by Samarn Nanthavanij and Samnieng Buspavanich.

Fluid Replacement in Acute Diarrheal Disease under Field Conditions, Chatrchai Watanakunakorn, Pratharn Chinayon, Kitti Hirunrus and Francis M. Morgan.

Studies by the U.S. Naval Medical Research Unit No. 2, Taipei, Taiwan. Conducted under the Auspices of the SEATO Cholera Research Project in Bangkok, Thailand, 1 April to 26 May, 1960, by Robert A. Phillips.

An Intestinal Biopsy Study in Acute Cholera and After Recovery, by H. Sprinz, R. Srifidadh, C. Benyajati, E. J. Gangarosa, W. R. Beisel, D. Kundel and S. B. Halstead.

A Study of Families in an Area where Cholera Occurred in Bangkok, Thailand, by Amara Chandrapanonda.

A Study of Salmonellae and Shigellae Isolated in Thailand during 1960, by Samarn Nanthavanij and Samnieng Buspavanich.

Parasitologic Sampling of Certain Regions of Thailand, by Oscar Felsenfeld.

Particularly significant in this work were the studies of the physiologic abnormalities in cholera patients, the nutritional evaluation, the identification and classification of **Vibrio cholerae** and other enteric pathogens, the lack of pathologic changes in the intestinal mucosa of cholera patients, the importance of fluid implementation under field conditions and patterns of spread of cholera in family groups. Dr. Robert Gordon, on assignment from the NIH, performed significant physiologic studies which showed that the intestinal mucosa in cholera patients was functionally intact. Work on the El Tor form of cholera highlighted this strain as an important pathogen. In addition to these achievements, the THAI SEATO Cholera Research Laboratory fathered a surprisingly large number of trainees who ultimately took very important positions as staff members, faculty members and highly qualified technicians in leading scientific centers.

Closing Acknowledgements

Commendation for this remarkable pioneering record is due many persons and it is possible to mention only a few. In no way does omission dampen the contribution of others.

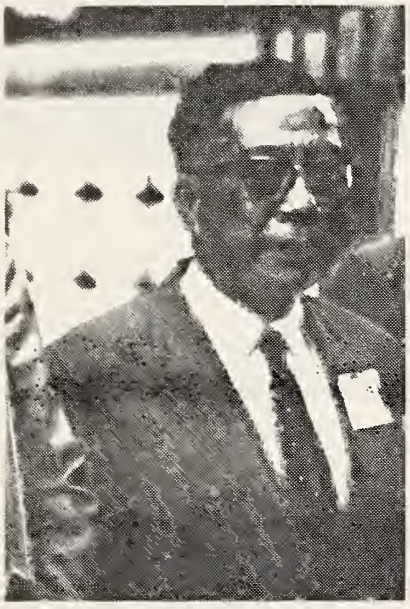

Figure 24. Dr. Luang Binbakya Bidyabhed (Pyn), Undersecretary of Health for Thailand and first Director General of SEATO Thai Cholera Research Laboratory. Picture taken in Dacca, December, 1960.

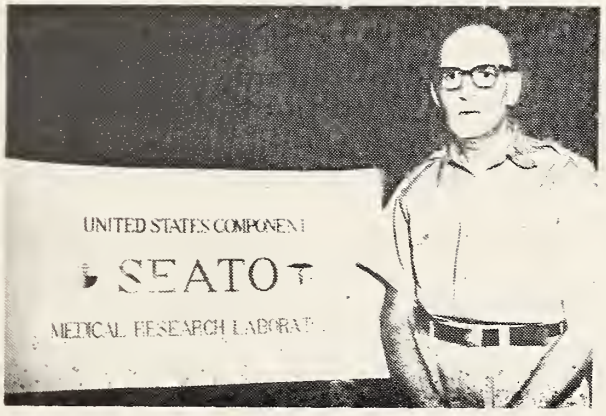

Figure 25. Oscar Felsenfeld, Lt. Col. MC, USAR. First Executive Director of Thailand SEATO Cholera Research Laboratory, Bangkok, 1959-1960.

Luang Binbakya Bidyabhed, M. D., Undersecretary of Health for Thailand and Director General of the Laboratory, accomplished so many things and opened so many important doors. Oscar Felsenfeld, Lt. Colonel, M.C., U.S.A.R., was Executive Director of the Laboratory who devotedly and expertly contributed directly to the scientific work and administrative details. Col. Richard P. Mason, M.C., Commandant of WRAIR, gave his full support which included financial and materiel resources. Col. Pung Pintuyothin, Royal Thai Army, Director of the Royal Thai Army Institute of Pathology, served as Laboratory Director. (See figure 17). Major Samnieng Buspabanich, Royal Thai Army and Chief of the Department of Bacteriology, directed the work of Thai laboratory personnel. (See figure 17) In addition to Captain Phillips, U.S.N., Captain Francis Morgan, M.C., U.S.N., of the NAMRU-2 unit, worked with the Bangkok project for a year. Commander Banyong Phabaramara, Royal Thai Army, served as epidemiologist for

the laboratory. Each of these officers contributed important epidemiologic findings. Dr. Eugene Gangarosa, Dr. Scott Halstead, Dr. William Beisel and Dr. Robert Gordon are excellent role examples of those young medical scientists from the United States who contributed importantly to the cholera laboratory program in Bangkok and who later assumed leadership roles elsewhere. (Gangarosa, Center for Disease Control, Atlanta; Halstead, Rockefeller Foundation; Beisel, Scientific Director, USAMRIID, Gordon, NIH). Dr. Charles (Chuck) Richards, ICA, and Dr. Clifford Pease, ICA, (International Cooperative Agency, later USAID) gave unstinting help in making the early organization of the laboratory possible and it was Dr. Pease who was instrumental in negotiating the initial financial award.

On December 23, 1960, following an exchange of diplomatic correspondence between Thailand and the United States, the title of and the responsibilities of the Thailand SEATO Cholera Research Laboratory were transferred to its successor, the SEATO Medical Research Laboratory with a United States and Thai component. The U.S. component became a field unit of WRAIR, functioning as a part of the Division of Communicable Disease and Immunology which provided technical supervision, administrative and material support. Non-expendable equipment was involved in this transfer at which time, the SEATO Medical Research Program assumed broader medical research responsibilities. These important events provided the fundamental base which ultimately led to the establishment of the Armed Forces Research Institute of Medical Science (AFRIMS) under the office of the Director, WRAIR.

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This brief account of the early events, which were the forerunner of the United States Armed Forces Research Centers in Malaysia and Thailand, is meant to serve as a stimulus for eventual preparation of factual and interpretative histories of these remarkable research laboratories. Each Center is an excellent example of the benefit which can accrue from collaborative bi-national research.

Each installation, the Armed Forces Medical Unit in Kuala Lumpur and the Armed Forces Research Institute of Medical Science (AFRIMS) in Bangkok, has contributed importantly to improvement of the health of the military services, the Asian people and the general public.

Gratitude is expressed to many scientists whose work made these notable developments possible. Never to be forgotten is the vision, dedication, selfless devotion and wise leadership of those persons who are no longer living.

Respectfully submitted,

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